Peroxisome proliferator activated receptor alpha activation decreases inflammatory and destructive responses in osteoarthritic cartilage

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Introduction

Although osteoarthritis (OA) was originally described as a non-inflammatory arthropathy, inflammatory responses in cartilage may contribute to disease progression. Cartilage degeneration may also be influenced by metabolic factors such as body mass index, plasma triglyceride levels, plasma cholesterol levels and vascular pathology. No drugs are available that inhibit cartilage degeneration in osteoarthritis. Peroxisome proliferator activated receptor α (PPARα) agonists such as fibrates are used in clinical practice as lipid lowering drugs and are also known to exert anti-inflammatory effects on various tissues. We hypothesized that PPARα agonists have anti-inflammatory and anti-destructive effects on human OA cartilage and we investigated this using OA cartilage explants in vitro.

Methods

Cartilage explants from six OA patients obtained with approval of the Local Ethical Committee (number MEC 2004-322), were cultured for 48 hours with 10 ng/ml interleukin (IL)1β as a pro-inflammatory stimulus without 100 µM Wy-14643, a potent and selective PPARα agonist. Gene expression of matrix metalloproteinase (MMP)1, MMP3, MMP13, collagen type II, aggrecan and PPARα in cartilage explants and the release of glycosaminoglycans, nitric oxide and prostaglandin E2 in the culture media were analyzed. A mixed linear model was used for the mRNA expression data and a univariate analysis of variance for the assays on the pooled media. To analyze the influence of interdonor differences in IL1β response, this factor was also fitted in the models as covariable.

Results

PPARα mRNA was expressed in the osteoarthritic cartilage. Addition of Wy-14643 decreased mRNA expression of MMP1 (p<0.001; Figure 1), MMP3 (p=0.01) and MMP13 (p<0.001; Figure 2) in cartilage explants that responded to IL1β, whereas Wy-14643 did not affect gene expression of collagen type II (p=1.00) and aggrecan (p=0.665). Finally, Wy-14643 inhibited the release of glycosaminoglycans (p=0.01) by cartilage explants in culture media (Figure 3).

Conclusion

PPARα agonist Wy-14643 inhibited MMP1, MMP3, MMP13 gene expression, nitric oxide and prostaglandin E2 production as well as glycosaminoglycan release but only in OA cartilage explants that responded to IL1β. Collagen type II or aggrecan mRNA expression were not affected. Besides the lipid lowering and anti-atherosclerotic effects of PPARα agonists that might be beneficial for the osteoarthritis disease process, PPARα agonists might also act anti-inflammatory and anti-destructive for osteoarthritic cartilage. This warrants further investigation of these drugs as a potential therapeutic strategy for OA.

Acknowledgements

All authors disclose any financial and personal relationships with other people or organisations that could inappropriately influence this work. This study/work was performed (partly) within the framework of the Dutch Top Institute Pharma project # T1-213. Stefan Clockaerts received a scholarschip of the University of Antwerp.